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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,690	08/28/2003	**Joanne Young Hee Kwak Kim**	112461-016	9043

73743 7590 10/08/2008

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/651,690	KIM ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11,13,16-27,29-34 and 36-283* is/are pending in the application.

4a) Of the above claim(s) *20-27, 41, 42, 70-72, 83-85, 112, 138, 164, 176, and 188-276* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims rejected are 1-4,6-11,13,16-19,29-34,36-40,43-69,73-82,86-111,113-137,139-163,165-175,177-187 and 277-283.

DETAILED ACTION

1. Applicant's response and amendments received December 26, 2007 are acknowledged.

Claims 1, 4, 6-8, 10, 16-19, 29-34, 36-40, 53, 73 and 151 have been amended.
Claims 5, 12, 14, 15, 28 and 35 have been canceled.
Claims 1-4, 6-11, 13, 16-27, 29-34, and 36-283 are pending.
Claims 20-27, 41, 42, 70-72, 83-85, 112, 138, 164, 176, and 188-276 stand withdrawn from consideration as being drawn to nonelected inventions. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the restriction requirement mailed August 25, 2004.

Claims 1-4, 6-11, 13, 16-19, 29-34, 36-40, 43-69, 73-82, 86-111, 113-137, 139-163, 165-175, 177-187 and 277-283 are under examination in the instant office action as they read on administering TNF-α antagonists.

Declaration under 37 CFR 1.183/1.131

2. The declaration filed on December 26, 2006 under 37 CFR 1.183 to suspend the rules concerning the requirement for all inventors to sign a declaration under 37 CFR 1.131 is acknowledged.

However, this petition was dismissed by Derek Woods in the office of petitions in the correspondence mailed March 12, 2008.

Since inventor Alan Beer has not signed the declaration and the rule requiring all inventors to sign has not been suspended in this application, applicant's showing under 37 CFR 1.131 is insufficient to antedate the prior art of Pluenneke. Thus this declaration has not overcome any rejection based upon the disclosure and teachings of Pluenneke.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. The rejection of claims 1-4, 8-15, 28-40, 43-69, 73-82, and 151 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of applicant's claim amendments received December 26, 2007 which more clearly indicate the metes and bounds of what is encompassed by the phrase "immune response" and fix the dependency error with claim 151.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 3, 48, 51, 55, 60, 63, 75, 88, 93, 96, 115, 120, 123, 141, 146, 149, 167, 172, 179, and 185 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The office action mailed June 27, 2007 states:

> Claims 3, 48, 51, 55, 60, 63, 75, 88, 93, 96, 115, 120, 123, 141, 146, 149, 167, 172, 179, and 185 have been amended to recite "wherein the ART includes all fertility treatments in which both eggs and sperm are handled". Again, applicant has not indicated where support for this limitation can be found. Lines 21-23 of page 1 of the specification disclose that ART includes in-vitro fertilization and other techniques, but it does not state that ART includes all techniques that require handling of eggs and sperm. As such, applicant's claim amendment appears to limit ART techniques to a particular subgenus of technologies that do not appear to be disclosed in the instant specification.

Applicant's arguments filed December 26, 2007 have been fully considered but they are not persuasive. Applicant argues that "it is well known in the art that ART includes all fertility treatments in which both eggs and sperm are handled" and provides a piece of art to support this position.

This argument is not persuasive because there is no argument that ART encompasses techniques wherein both eggs and sperm are handled. However, the term ART also encompasses other techniques such as artificial insemination which do not require handling both types of gametes. As such the claims recite a particular subgenus of all the techniques encompassed by ART, namely those that manipulate both eggs and sperm. Direction to this broad subgenus could not be located by the examiner in the specification, nor does applicant's reply indicate where the breadth of this subgenus is disclosed for use in the instant methods. Note that disclosure of the species of in vitro fertilization, an ART technique that manipulates both eggs and sperm is only a species of the recited subgenus. Since the subgenus itself does not appear to be disclosed in the application as filed, the rejection is maintained.

7. The rejection of claims 1-19, 28-40, 43-69, and 73-82 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement has been withdrawn in view of applicant's claim limitations received December 26, 2007.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 86, 89-91, 94, 98-100, 103-111,113, 116-118, 121, 125, 126, 129-137, 139, 142-44, 147, 151-153, 155-163, 165, 168-170, 173, and 174 stand rejected under 35 U.S.C. 103(a), as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) for the reasons of record. The office action mailed November 29, 2005 states:

> Pluenneke discloses the use of agents that inhibit the activity or production of TNF-α in the treatment of many medical disorders (see entire document, particularly the abstract and paragraphs 8 and 9). Examples of TNF-α inhibiting agents that are useful in the methods disclosed by Pluenneke include the TNFR-Ig construct etanercept, as well as anti-TNF-α monoclonal antibodies including, but not limited to, infliximab, D2E7, and CDP571, as well as the TNF-α synthesis inhibitor pentoxyfilline (see particularly paragraphs 9, 19, 20, and 32). These reagents are to be used in treating disorders of the human female reproductive system and include multiple implant failure/infertility and spontaneous abortion (see particularly paragraph 73). It should be noted that methods that inhibit spontaneous abortion or infertility necessarily enhance the ability of a subject to carry an embryo to term. Suitable dosages and routes of administration for the reagents disclosed by Pluenneke are provided (see particularly paragraphs 26-32). Note the reagents can be administered once or multiple times (see particularly paragraph 29). The disclosed dosage ranges for etanercept and the anti-TNF-α monoclonal antibodies overlap with the ranges claimed by applicant, and these agents can be injected intravenously, intramuscularly, subcutaneously, or can be administered as aerosols, eyedrops, oral medications including pills, or topical forms such as lotions, gels, sprays or ointments (see particularly paragraph 26). Patient populations included for treatment using the methods and compositions of Pluenneke include both humans and non-human animals (see particularly paragraph 81).
>
> Animals have immune systems, and as such they will all have a population of Th1 and Th2 cells, and thus they necessarily comprise a Th1 to Th2 ratio. The teachings of Pluenneke provide methods and compositions to antagonize the Th1 cytokine TNF-α, and as such these methods necessarily alter the Th1 to Th2 ratio present in the subject being treated. These teachings differ from the claimed invention in that they do not teach the administration of the TNF-α antagonist prior to conception, or the administration of a TNF-α antagonist combined with lymphocyte immunization, intravenous IgG, anticoagulants or steroids such as prednisone.
>
> Coulam et al. teaches methods and clinical protocols for use in diagnosing and treating patients that suffer from recurrent spontaneous abortions (see entire document, particularly the introduction). These methods include the administration of heparin, aspirin, prednisone, intravenous Ig, and immunization with paternal lymphocytes to treat such patients (see particularly Table IV). The methods of Coulam et al. only specify IVIg and not a specific Ig isotype, but the most abundant isotype in blood plasma is IgG, and as such Coulam et al. teach the administration of IgG to patients (see particularly the paragraph that spans pages 3.2 and 3.3 of Janeway et al. and the paragraph that spans pages 67 to 68 of Coulam et al.). Table IV of Coulam et al. indicates that many of the therapeutic interventions may or must be initiated before conception, such therapies including the use of aspirin, prednisone, and therapeutic immunization with lymphocytes (see particularly the first full paragraph of page 67 and Table IV). All of these treatments initiated prior to conception are intended to increase the odds that a successful conception and delivery to term will result (see particularly from the middle of the right column of page 66 to the end of the left column of page 67). Indeed, Coulam et al. specifically state that initiating immunotherapy preconceptually as compared with postconceptually offers the advantage of significantly increase live birth rates (see particularly the first full sentence of the left column of page 68).

> Both Pluenneke and Coulam et al. teach methods and composition that treat spontaneous abortion and infertility. As such, "It is *prima facie* obvious to combine two compositions (or methods) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).
>
> It would also have been *prima facie* obvious to a person of ordinary skill in the art to administer just the TNF-α antagonists of Pluenneke prior to conception. A person of ordinary skill in the art would have been motivated to administer just the TNF-α antagonist at this time based upon the teachings of Coulam et al. that many therapeutic interventions are initiated prior to conception in order to increase the odds of achieving a successful conception and pregnancy, and that doing so significantly increases live birth rates. Therefore, initiating treatment with a TNF-α antagonist prior to conception would gain the advantage of increasing the probability that the therapeutic intervention would be successful in inhibiting spontaneous abortion or implantation failure as evidenced by an increased live birth rate.

Applicant's arguments filed December 26, 2007 have been fully considered but they are not persuasive. Applicant argues that the declaration submitted December 26, 2007 is sufficient to antedate the art of Pluenneke and thus all rejections utilizing this art have been obviated.

This argument is not persuasive for the reasons discussed supra concerning applicant's declaration submitted December 26, 2007.

The rejection is maintained.

10. Claims 177, 180-183, and 186 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) as applied to claims 86, 89-91, 94, 98-100, 103-111,113, 116-118, 121, 125, 126, 129-137, 139, 142-44, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) for the reasons of record.

The office action mailed November 29, 2005 states:

> The teachings of Pluenneke, Coulam et al. and Janeway et al. have been discussed above. These teachings differ from the claimed invention in that Pluenneke does not disclose the anti-TNFα monoclonal antibody CDP870 as part of his non-limiting examples of anti-TNFα antibodies that are suitable for use in methods of treating infertility and spontaneous abortion.
>
> Athwal et al. disclose the creation of the anti-TNFα antibody CDP870 (see entire document, particularly Figure 22 and paragraphs 231-266). This antibody is capable of neutralizing TNF-α and is comparable in efficacy to etanercept (see particularly paragraph 262). CDP870 is disclosed as being PEGylated, and as such it has a long plasma half life that is desirable for the treatment of patients (see particularly paragraphs 67 and 26).

> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Athwal et al. for the anti-TNFα reagents, such as etanercept, used in the methods of Pluenneke with modified timing of administration as taught by Coulam et al. Motivation to make this substitution comes from the teachings of Athwal et al. that increased plasma half life of a reagent is desirable for treating patients and that CDP870 is PEGylated to increase its plasma half life. Therefore, a person of ordinary skill in the art would have been motivated to use CDP870 in the methods of Pluenneke et al. as modified by Coulam et al. since CDP870 has a comparable efficacy to etanercept, and since CDP870 has the advantage of being PEGlylated to increase its half life, thus making CDP870 an ideal reagent for treating patients as taught by Athwal et al.

Applicant's arguments filed December 26, 2007 have been fully considered but they are not persuasive. Applicant argues that the declaration submitted December 26, 2007 is sufficient to antedate the art of Pluenneke and thus all rejections utilizing this art have been obviated.

This argument is not persuasive for the reasons discussed supra concerning applicant's declaration submitted December 26, 2007.

The rejection is maintained.

11. Claims 101, 102, 127, 128, 154, 175, and 280-282 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) as applied to claims 86, 89-91, 94, 98-100, 103-111,113, 116-118, 121, 125, 126, 129-137, 139, 142-44, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of in view of Terao et al. (US Patent No. 6,013,252, see entire document, of record) for the reasons of record.

The office action mailed November 29, 2005 states:

> The teachings of Pluenneke, Coulam et al. and Janeway et al. have been discussed above. These teachings differ from the claimed invention in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.
>
> Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).
>
> Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy) as taught by Pluenneke and modified by the teachings of Coulam et al. and Janeway et al., into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al.

that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient.

Applicant's arguments filed December 26, 2007 have been fully considered but they are not persuasive. Applicant argues that the declaration submitted December 26, 2007 is sufficient to antedate the art of Pluenneke and thus all rejections utilizing this art have been obviated.

This argument is not persuasive for the reasons discussed supra concerning applicant's declaration submitted December 26, 2007.

The rejection is maintained.

12. Claims 187 and 283 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) and in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) as applied to claims 86, 89-91, 94, 98-100, 103-111,113, 116-118, 121, 125, 126, 129-137, 139, 142-44, 147, 151-153, 155-163, 165, 168-170, 173, 174, 177, 180-183, and 186 above, and further in view of in view of Terao et al. (US Patent No. 6,013,252, see entire document, of record) for the reasons of record. The office action mailed November 29, 2005 states:

The teachings of Pluenneke, Coulam et al., Janeway et al. and Athwal et al. have been discussed above. These teachings differ from the claimed invention as recited in claims 187 and 283 in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.

Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors of Pluenneke and Athwal et al. that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy) with the timing of administration modified by the teachings of Coulam et al., into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient.

Applicant's arguments filed December 26, 2007 have been fully considered but they are not persuasive. Applicant argues that the declaration submitted December 26,

2007 is sufficient to antedate the art of Pluenneke and thus all rejections utilizing this art have been obviated.

This argument is not persuasive for the reasons discussed supra concerning applicant's declaration submitted December 26, 2007.

The rejection is maintained.

13. Claims 1, 6, 13, 16-19, 29-34, 36-39, 43-46, 49, 53, 56-58, 61, 65-68, 73, and 76-81 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) as applied to claims 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) and further in view of Le et al. (US patent 5,656,272, see entire document) for the reasons of record.

The office action mailed June 27, 2008 states:

> The teachings of Pluenneke, Coulam et al. and Janeway et al. have been discussed above. In summary, these teachings indicate that all women suffering from disorders of the female reproductive system such as multiple implant failure/infertility and spontaneous abortion should be treated with TNF-α antagonists, and that treatment is most effective when it begins prior to conception. These teachings differ from the claimed invention in that they do not disclose the measurement of the Th1 to Th2 ratio in patients being treated for spontaneous abortions or infertility prior and subsequent to treatment with a therapeutic agent.
>
> Raghupathy et al. teach that significantly greater levels of the Th2 cytokines IL-6 and IL-10 were found in normal pregnancy as compared to women with a history of unexplained recurrent spontaneous abortions (RSA), and that significantly higher levels of the Th1 cytokine IFN-γ were found in RSA as compared to normal pregnancy (see entire document, particularly the abstract). Raghupathy et al. calculated the ratio of Th2 to Th1 cytokines because the ratio of these cytokines is more important than their mere presence or absence (see particularly the left column of page 125, the first full paragraph of the left column of page 127, and Table 1). Their data demonstrates a distinctly increased Th2 bias in normal pregnancy and an increased Th1 bias in RSA (see particularly the first full paragraph of the left column of page 127). The cytokines measured by Raghupathy et al. include the Th2 cytokines IL-4, IL-5, IL-6, IL-10, and the Th1 cytokines IL-2, IFN-γ, TNF-β and TNF-α (see particularly the section titled Cytokine profiles in MLPR on page 124). One particular ratio calculated by Raghupathy et al. was IL-10:TNF-α, although ratios comparing any of the cytokines measured by Raghupathy would have been obvious to calculate (see particularly Table 1). These cytokines are disclosed as having been measured from PBMC stimulated *in vitro* with either irradiated placental cells (MLPR) or soluble

antigen (see particularly the materials and methods section) or alternatively, the cytokines were measured directly from patient sera (see particularly the first full paragraph of page 129). Serum cytokine measurements indicated significantly increased IL-6 and IL-10 levels in normal pregnancy as compared to RSA, with significantly increased TNF-α detected in serum from recurrent aborters (see particularly the first full paragraph of page 129).

Raghupathy et al. further teach that appropriate interventions that shift the ratio of immune reactivity toward Th2 dominance or that inhibit Th1 cytokine production are to be administered to patients to help them achieve a successful pregnancy, and that not all women suffering from RSA demonstrate an immunological etiology such as an increased level of Th1 cytokines (see particularly the last two paragraphs of page 129). As such, the identification of patients that have altered cytokine ratios would allow for the more efficacious targeting of immunological therapeutic interventions to only the subset of patients who are likely to be responsive to such interventions (see particularly the last two paragraphs of page 129).

Le et al. teach that measuring cytokines obtained from patients before and after treatment with anti-TNF-α antibodies is one way to determine the clinically efficacy of treating a disease or condition by administering anti-TNF-α antibodies (see entire document, particularly Example XXII, Table 9A and the paragraph spanning columns 77 and 78).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the Th1 to Th2 ratio of patients as taught by Raghupathy et al. before performing the therapeutic methods of Pluenneke as modified by Coulam et al. Motivation to incorporate this method step comes from the teachings of Raghupathy et al. that not all cases of spontaneous abortion have an immunological etiology, but in those cases that do, therapeutic methods designed to alter the Th1 to Th2 ratio are useful in helping such women achieve a successful pregnancy. As such, incorporation of a screening method to identify women that suffer spontaneous abortion of immunological etiology into the treatment methods collectively taught by Pluenneke as modified by Coulam et al. would offer the advantage of targeting immunotherapy to only those patients that are likely to benefit from such interventions. A person of ordinary skill in the art would have also been motivated to repeat the measurement of the Th1 to Th2 ration to determine if the administered agent was having the expected therapeutic effect as was taught by Le et al. As such, repeated determinations of the Th1 to Th2 ratio allows for the initial selection of patients likely to benefit from treatment and provides an indication as to the efficacy of the selected treatment method.

Applicant's arguments filed December 26, 2007 have been fully considered but they are not persuasive. Applicant argues that the declaration submitted December 26, 2007 is sufficient to antedate the art of Pluenneke and thus all rejections utilizing this art have been obviated.

This argument is not persuasive for the reasons discussed supra concerning applicant's declaration submitted December 26, 2007.

The rejection is maintained.

14. Claims 40, 69, and 82 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire

document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) and in view of Le et al. (US patent 5,656,272, see entire document) as applied to claims 1, 6, 13, 16-19, 29-34, 36-39, 43-46, 49, 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) for the reasons of record.

The office action mailed June 27, 2007 states:

> The teachings of Pluenneke, Coulam et al., Janeway et al., Raghupathy et al. and Le et al. have been discussed above. These teachings differ from the claimed invention in that they do not disclose the use of the anti-TNF-α antibody CDP870.
>
> Athwal et al. disclose the creation of the anti-TNFα antibody CDP870 (see entire document, particularly Figure 22 and paragraphs 231-266). This antibody is capable of neutralizing TNF-α and is comparable in efficacy to etanercept (see particularly paragraph 262). CDP870 is disclosed as being PEGylated, and as such it has a long plasma half life that is desirable for the treatment of patients (see particularly paragraphs 67 and 26).
>
> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Athwal et al. for the anti-TNFα reagents, such as etanercept, used in the methods of collectively taught by Pluenneke, Coulam et al., Janeway et al., Raghupathy et al. and Le et al. Motivation to make this substitution comes from the teachings of Athwal et al. that increased plasma half life of a reagent is desirable for treating patients and that CDP870 is PEGylated to increase its plasma half life. Therefore, a person of ordinary skill in the art would have been motivated to use CDP870 in place of other TNF-α antagonists because CDP870 has a comparable efficacy to etanercept, and since CDP870 has the advantage of being PEGlylated to increase its half life, thus making CDP870 an ideal reagent for treating patients as taught by Athwal et al.

Applicant's arguments filed December 26, 2007 have been fully considered but they are not persuasive. Applicant argues that the declaration submitted December 26, 2007 is sufficient to antedate the art of Pluenneke and thus all rejections utilizing this art have been obviated.

This argument is not persuasive for the reasons discussed supra concerning applicant's declaration submitted December 26, 2007.

The rejection is maintained.

15. Claims 2-4, 7-11, 47, 48, 50-52, 54, 55, 59, 60, 62-64, 74, 75, 87, 88, 92, 93, 95-97, 114, 115, 119, 120, 122-124, 140, 141, 145, 146, 148-150, 166, 167, 171, 172, 178,

179, 184, and 185 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) in view of Le et al. (US patent 5,656,272, see entire document) and in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) as applied to claims 1, 6, 13, 16-19, 29-34, 36-40, 43-46, 49, 53, 56-58, 61, 65-69, 73, 76-82, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Ng et al. (Am. J. Reproductive Immunol., 2002, 48:77-86, Presented at the ASRI XXIst Annual Meeting in Chicago, June 9-12 2001, of record on PTO form 1449 filed May 19, 2004) as evidenced by Alak et al. (US patent No. 5,693,534, see entire document) for the reasons of record.

The office action mailed June 27, 2007 states:

> The teachings of Pluenneke, Coulam et al., Janeway et al., Raghupathy et al., Le et al. and Athwal et al. have been discussed above. These teachings differ from the instant claimed invention in that they do not disclose measuring the Th1 to Th2 cytokine ratio using absolute cell counts or by intracellular cytokine staining. These teachings also do not explicitly indicate the treatment of the patients that have undergone the specific assisted reproductive technologies of *in vitro* fertilization or ovulation induction cycles.
>
> Ng et al. teach that there are changes in both absolute counts of T cells that express Th1 and Th2 cytokines, as well as changes in the ratio of these cytokines, when comparing women diagnosed with recurrent spontaneous abortions or who had multiple implantation failures after *in vitro* fertilization and embryo transfer (IVF/ET) with normal pregnancy controls (see entire document, particularly the abstract). Ovulation induction is a routine part of IVF therapy that increases the number of eggs that are retrieved and available for use in IVF therapy, and as such women that have undergone IVF have also undergone ovulation induction therapy (see Alak et al., particularly column 5, lines 16-34). The data obtained by Ng et al. was collected by intracellular cytokine staining of PBMC isolated from study participants (see particularly the Materials and Methods section). Ng et al. demonstrated that the absolute T cell counts of TNF-α expressing CD3+/CD4+ T cells were significantly increased in implantation failure patients as compared to normal controls (see particularly the paragraph that spans pages 80 and 81). Ng et al. also disclose that increased Th1/Th2 cytokine ratios were observed in women with recurrent pregnancy losses and multiple implantation failures after IVF/ET as compared with normal controls (see particularly the paragraph that spans the right and left columns of page 78). Cytokine ratios compared by Ng et al. include INF-γ/IL-4, INF-γ/IL-10, TNF-α/IL-4, TNF-α/IL10 (see particularly the final paragraph of the results section on page 82). Of these the ratio of TNF-α to IL-10 appeared most important since patients with implantation failures after IVF/ET had an up-regulated TNF-α level and a down-regulated IL-10 level as compared to controls (see

particularly Table III, the first paragraph of the discussion on page 82, the paragraph that spans pages 83-84, and the penultimate paragraph on page 84).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to substitute the cytokine detection methods and patient populations taught by Ng et al. for the methods taught collectively by the teachings of Pluenneke, Coulam et al., Janeway et al., Raghupathy et al., Le et al. and Athwal et al. Motivation to make these substitutions comes from Raghupathy et al.'s teachings that it is important to identify women suffering from spontaneous abortion that would benefit from immunological interventions that alter a woman's Th1 to Th2 ratio, and Ng et al.'s teaching of methods that use intracellular cytokine staining and absolute cell counts to identify additional women, such as those undergoing IVF/ET, that would benefit from interventions that alter the Th1 to Th2 ratio. A person of ordinary skill in the art would also have been motivated at the time the invention was made to reduce the absolute counts of CD3+/CD4+ T cells that express TNF-α since this population was shown by Ng et al. to be increased in patients that suffer spontaneous abortions and implantation failure, and the teachings of Pluenneke that methods that suppress the expression of TNF-α are to be used in treating conditions mediated by increased levels of TNF-α, such conditions including multiple implant failure/infertility and spontaneous abortion.

Applicant's arguments filed December 26, 2007 have been fully considered but they are not persuasive. Applicant argues that the declaration submitted December 26, 2007 is sufficient to antedate the art of Pluenneke and thus all rejections utilizing this art have been obviated.

This argument is not persuasive for the reasons discussed supra concerning applicant's declaration submitted December 26, 2007.

The rejection is maintained.

16. Claims 101, 102, 127, 128, 154, 175, and 277-283 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) in view of Le et al. (US patent 5,656,272, see entire document) and in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) in view of Ng et al. (Am. J. Reproductive Immunol., 2002, 48:77-86, Presented at the ASRI XXIst Annual Meeting in Chicago, June 9-12 2001, of record on PTO form 1449 filed May 19, 2004) as evidenced by Alak et al. (US patent No. 5,693,534, see entire document) as

applied to claims 1-4, 6-11, 13, 16-19, 29-34, 36-40, 43-69, 73-82, 86-100, 103-111, 113-126, 129-137, 139-153, 155-163, 165-174 above, and further in view of Terao et al. (US Patent No. 6,013,252, of record) for the reasons of record.

The office action mailed June 27, 2007 states:

> The collective teachings of Pluenneke, Coulam et al., Raghupathy et al., Le et al., Athwal et al., and Ng et al. have been discussed above. These teachings differ from the claimed invention in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.
>
> Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).
>
> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors in a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other forms that can be applied vaginally offer the advantage of being easily administered to the patient.

Applicant's arguments filed December 26, 2007 have been fully considered but they are not persuasive. Applicant argues that the declaration submitted December 26, 2007 is sufficient to antedate the art of Pluenneke and thus all rejections utilizing this art have been obviated.

This argument is not persuasive for the reasons discussed supra concerning applicant's declaration submitted December 26, 2007.

The rejection is maintained.

17. Claims 113, 116-118, 121, 125-126, and 129-137 stand rejected under 35 U.S.C. 103(a), as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) for the reasons of record.

The office action mailed June 27, 2007 states:

> Finck discloses the use of agents that inhibit the activity or production of TNF-α in the treatment of many medical disorders (see entire document, particularly the abstract and page 1). Examples of TNF-α inhibiting agents that are useful in the methods disclosed by Finck include the TNFR-Ig construct etanercept, as well as anti-TNF-α monoclonal antibodies and the TNF-α synthesis inhibitor pentoxyfilline (see particularly pages 4 and 5). These reagents are to be used in treating disorders of the human female reproductive system and include multiple implant failure/infertility and spontaneous abortion (see particularly page 15). It should be noted that methods that inhibit spontaneous abortion or infertility necessarily enhance the ability of a subject to carry an embryo to term. Suitable dosages, routes, and frequency of administration for the

reagents disclosed by Finck are provided (see particularly page 8). Note that the reagents of Finck can be administered once or multiple times (ibid). TNF-α inhibitors are disclosed as being administered by many routes, including intravenously, intramuscularly, subcutaneously, or as aerosols, eyedrops, oral medications including pills, or topical forms such as lotions, gels, sprays or ointments (see particularly page 7). Patient populations included for treatment using the methods and compositions of Pluenneke include both humans and non-human animals (see particularly paragraph 81).

Animals have immune systems, and as such they will all have a population of Th1 and Th2 cells, and thus they comprise a Th1 to Th2 ratio. The teachings of Finck provide methods and compositions to antagonize the Th1 cytokine TNF-α, and as such these methods alter the Th1 to Th2 ratio present in the subject being treated. These teachings differ from the claimed invention in that they do not teach the administration of the TNF-α antagonist prior to conception, or the administration of a TNF-α antagonist combined with lymphocyte immunization, intravenous IgG, anticoagulants or steroids such as prednisone.

Coulam et al. teaches methods and clinical protocols for use in diagnosing and treating patients that suffer from recurrent spontaneous abortions (see entire document, particularly the introduction). These methods include the administration of heparin, aspirin, prednisone, intravenous Ig, and immunization with paternal lymphocytes to treat such patients (see particularly Table IV). The methods of Coulam et al. specify IVIg, but given that the most abundant isotype in blood plasma is IgG, Coulam et al. teach the administration of IgG to patients (see particularly the paragraph that spans pages 3.2 and 3.3 of Janeway et al. and the paragraph that spans pages 67 to 68 of Coulam et al.). Table IV of Coulam et al. indicates that many of the therapeutic interventions may or must be initiated before conception, such therapies including the use of aspirin, prednisone, and therapeutic immunization with lymphocytes (see particularly the first full paragraph of page 67 and Table IV). All of these treatments initiated prior to conception are intended to increase the odds that a successful conception and delivery to term will result (see particularly from the middle of the right column of page 66 to the end of the left column of page 67). Indeed, Coulam et al. specifically state that initiating immunotherapy preconceptually as compared with postconceptually offers the advantage of significantly increasing live birth rates (see particularly the first full sentence of the left column of page 68).

Both Finck and Coulam et al. teach methods and composition that treat spontaneous abortion and infertility. As such, "It is *prima facie* obvious to combine two compositions (or methods) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

It would also have been *prima facie* obvious to a person of ordinary skill in the art to administer the TNF-α antagonists of Pluenneke prior to conception. A person of ordinary skill in the art would have been motivated to administer just the TNF-α antagonist at this time based upon the teachings of Coulam et al. that many therapeutic interventions are initiated prior to conception in order to increase the odds of achieving a successful conception and pregnancy, and that doing so significantly increases live birth rates. Therefore, initiating treatment with a TNF-α antagonist prior to conception would gain the advantage of increasing the probability that the therapeutic intervention would be successful in inhibiting spontaneous abortion or implantation failure as evidenced by an increased live birth rate.

Applicant's arguments filed December 27, 2007 have been fully considered but they are not persuasive. Applicant argues that independent claims 53 and 73 have been amended to recite additional steps not disclosed by the cited references.

This argument is not persuasive because claims 53 and 73 are not part of this rejection and thus applicant is arguing limitations not claimed.

18. Claims 127 and 128 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) as applied to claims 113, 116-118, 121, 125-126, and 129-137 above, and further in view of in view of Terao et al. (of record) for the reasons of record.

The office action mailed June 27, 2007 states:

> The teachings of Finck and Coulam et al. have been discussed above. These teachings differ from the claimed invention in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.
>
> Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).
>
> Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy) as taught by Finck and Coulam et al. into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient

Applicant's arguments filed December 27, 2007 have been fully considered but they are not persuasive. Applicant argues that independent claims 53 and 73 have been amended to recite additional steps not disclosed by the cited references.

This argument is not persuasive because claims 53 and 73 are not part of this rejection and thus applicant is arguing limitations not claimed.

19. Claims 1, 6, 13, 16-19, 29-34, 36, 37, 43-46, 49, 53, 56-58, 61, 65, 66, 73, 76-79, 86, 89-91, 94, 98-111, and 277-280 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) and in view of Terao et al. (of record) as applied to claims 113, 116-118, 121, and 125-137 above, and further in view of Raghupathy et al. (of record) and in view of Le et al (US patent 5,656,272) for the reasons of record.

The office action mailed June 27, 2007 states:

The teachings of Finck, Coulam et al., and Terao et al. have been discussed above. In summary, these teachings indicate that all women suffering from disorders of the female reproductive system such as multiple implant failure/infertility and spontaneous abortion should be treated with TNF-α antagonists, and that treatment is most effective when it begins prior to conception. These teachings differ from the claimed invention in that they do not teach the measurement of a Th1 to Th2 ratio prior and subsequent to initiating treatment with a TNF-α inhibitor.

Raghupathy et al. teach that significantly greater levels of the Th2 cytokines IL-6 and IL-10 were found in normal pregnancy as compared to women with a history of unexplained recurrent spontaneous abortions (RSA), and that significantly higher levels of the Th1 cytokine IFN-γ were found in RSA as compared to normal pregnancy (see entire document, particularly the abstract). Raghupathy et al. calculated the ratio of Th2 to Th1 cytokines because the ratio of these cytokines is more important than their mere presence or absence (see particularly the left column of page 125, the first full paragraph of the left column of page 127, and Table 1). Their data demonstrates a distinctly increased Th2 bias in normal pregnancy and an increased Th1 bias in RSA (see particularly the first full paragraph of the left column of page 127). The cytokines measured by Raghupathy et al. include the Th2 cytokines IL-4, IL-5, IL-6, IL-10, and the Th1 cytokines IL-2, IFN-γ, TNF-β and TNF-α (see particularly the section titled Cytokine profiles in MLPR on page 124). One particular ratio calculated by Raghupathy et al. was IL-10:TNF-α, although ratios comparing any of the cytokines measured by Raghupathy would have been obvious to calculate (see particularly Table 1). These cytokines are disclosed as having been measured from PBMC stimulated *in vitro* with either irradiated placental cells (MLPR) or soluble antigen (see particularly the materials and methods section) or alternatively, the cytokines were measured directly from patient sera (see particularly the first full paragraph of page 129). Serum cytokine measurements indicated significantly increased IL-6 and IL-10 levels in normal pregnancy as compared to RSA, with significantly increased TNF-α detected in serum from recurrent aborters (see particularly the first full paragraph of page 129).

Raghupathy et al. further teach that appropriate interventions that shift the ratio of immune reactivity toward Th2 dominance or that inhibit Th1 cytokine production are to be administered to patients to help them achieve a successful pregnancy, and that not all women suffering from RSA demonstrate an immunological etiology such as an increased level of Th1 cytokines (see particularly the last two paragraphs of page 129). As such, the identification of patients that have altered cytokine ratios would allow for the more efficacious targeting of immunological therapeutic interventions to only the subset of patients who are likely to be responsive to such interventions (see particularly the last two paragraphs of page 129).

Le et al. teach that measuring cytokines obtained from patients before and after treatment with anti-TNF-α antibodies is one way to determine the clinically efficacy of treating a disease or condition by administering anti-TNF-α antibodies (see entire document, particularly Example XXII, Table 9A and the paragraph spanning columns 77 and 78). One specific anti-TNF-α antibody disclosed by Le et al. is cA2, also known as infliximab/Remicade®, which has the advantageous properties of not crossreacting with related antigens, such as TNF-β, and safe, successful in vivo human use (see particularly the middle of column 20 and Examples XVI-XXIII).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the Th1 to Th2 ratio of patients as taught by Raghupathy et al. before performing initiating therapy with a TNF-α inhibitor. Motivation to do so comes from the teachings of Raghupathy et al. that not all cases of spontaneous abortion have an immunological etiology, but in those cases that do, therapeutic methods designed to alter the Th1 to Th2 ratio are useful in helping such women achieve a successful pregnancy. As such, incorporation of a screening method to identify women that suffer spontaneous abortion of immunological etiology into the treatment method would offer the advantage of targeting immunotherapy to only those patients that are likely to benefit from such interventions. A person

> of ordinary skill in the art would have also been motivated to repeat the measurement of the Th1 to Th2 ratio to determine if the administered agent was having the expected therapeutic effect as was taught by Le et al. As such, repeated determinations of the Th1 to Th2 ratio allows for the initial selection of patients likely to benefit from treatment and provides an indication as to the efficacy of the selected treatment method. Further, it would have been obvious to a person of ordinary skill in the art to use the anti-TNF-α antibody of Le et al. in methods of treating infertility because Le et al. disclose that there antibody does not crossreact with other cytokines such as TNF-β and that it can be safely and successfully used in vivo in humans.

Applicant's arguments filed December 27, 2007 have been fully considered but they are not persuasive. Applicant argues that independent claims 53 and 73 have been amended to recite additional steps not disclosed by the cited references, specifically measuring a ratio of a Th1 to a Th2 cytokine, the Th1 and Th2 cytokines consisting of TNFα.

This argument is not persuasive because the cited references do disclose measuring cytokine ratios as discussed in the rejection of record. Further, TNFα cannot logically be both a Th1 and a Th2 cytokine, and this point is evidenced by independent claims 1, 53, and 73 which specifically recited which cytokines are to be considered Th1 and which are Th2. Note that TNFα appears only in the Th1 list. Thus applicant has argued limitations not claimed.

20. Claims 2-4, 7-11, 47, 48, 50-52, 54, 55, 59, 60, 62-64, 74, 75, 87, 88, 92, 93, 95-97, 114, 115, 119, 120, and 122-124 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) in view of Terao et al. (of record) in view of Raghupathy et al. (of record) and in view of Le et al. (US patent 5,656,272) as applied to claims 1, 6, 13, 16-19, 29-34, 36, 37, 43-46, 49, 53, 56-58, 61, 65, 66, 73, 76-79, 86, 89-91, 94, 98-111, 113, 116-118, 121, 125-137 and 277-280 above, and further in view of Ng et al. (of record) as evidenced by Alak et al. (of record) for the reasons of record. The office action mailed June 27, 2007 states:

> The teachings of Finck, Coulam et al., Raghupathy et al., and Le et al. have been discussed above. These teachings differ from the instant claimed invention in that they do not disclose measuring the Th1 to Th2 cytokine ratio using absolute cell counts or by intracellular cytokine staining. These teachings also do not explicitly indicate the treatment of the patients that have undergone the specific assisted reproductive technologies of *in vitro* fertilization or ovulation induction cycles.

Ng et al. teach that there are changes in both absolute counts of T cells that express Th1 and Th2 cytokines, as well as changes in the ratio of these cytokines, when comparing women diagnosed with recurrent spontaneous abortions or who had multiple implantation failures after *in vitro* fertilization and embryo transfer (IVF/ET) with normal pregnancy controls (see entire document, particularly the abstract). Ovulation induction is a routine part of IVF therapy that increases the number of eggs that are retrieved and available for use in IVF therapy, and as such women that have undergone IVF have also undergone ovulation induction therapy (see Alak et al., particularly column 5, lines 16-34). The data obtained by Ng et al. was collected by intracellular cytokine staining of PBMC isolated from study participants (see particularly the Materials and Methods section). Ng et al. demonstrated that the absolute T cell counts of TNF-α expressing CD3+/CD4+ T cells were significantly increased in implantation failure patients as compared to normal controls (see particularly the paragraph that spans pages 80 and 81). Ng et al. also disclose that increased Th1/Th2 cytokine ratios were observed in women with recurrent pregnancy losses and multiple implantation failures after IVF/ET as compared with normal controls (see particularly the paragraph that spans the right and left columns of page 78). Cytokine ratios compared by Ng et al. include INF-γ/IL-4, INF-γ/IL-10, TNF-α/IL-4, TNF-α/IL10 (see particularly the final paragraph of the results section on page 82). Of these the ratio of TNF-α to IL-10 appeared most important since patients with implantation failures after IVF/ET had an up-regulated TNF-α level and a down-regulated IL-10 level as compared to controls (see particularly Table III, the first paragraph of the discussion on page 82, the paragraph that spans pages 83-84, and the penultimate paragraph on page 84).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to use the cytokine detection methods and patient populations taught by Ng et al. in the methods collectively taught by Finck, Coulam et al., Raghupathy et al., and Le et al. Motivation to do so comes from Raghupathy et al.'s teachings that it is important to identify women suffering from spontaneous abortion that would benefit from immunological interventions that alter a woman's Th1 to Th2 ratio, and Ng et al.'s teaching of methods that use intracellular cytokine staining and absolute cell counts to identify additional women, such as those undergoing IVF/ET, that would benefit from interventions that alter the Th1 to Th2 ratio. A person of ordinary skill in the art would also have been motivated at the time the invention was made to reduce the absolute counts of CD3+/CD4+ T cells that express TNF-α since this population was shown by Ng et al. to be increased in patients that suffer spontaneous abortions and implantation failure, and the teachings of Finck that methods that suppress the expression of TNF-α are to be used in treating conditions mediated by increased levels of TNF-α, such conditions including multiple implant failure/infertility and spontaneous abortion.

Applicant's arguments filed December 27, 2007 have been fully considered but they are not persuasive. Applicant argues that independent claims 53 and 73 have been amended to recite additional steps not disclosed by the cited references, specifically measuring a ratio of a Th1 to a Th2 cytokine, the Th1 and Th2 cytokines consisting of TNFα.

This argument is not persuasive because the cited references do disclose measuring cytokine ratios as discussed in the rejection of record. Further, TNFα cannot logically be both a Th1 and a Th2 cytokine, and this point is evidenced by independent claims 1, 53, and 73 which specifically recited which cytokines are to be considered Th1

and which are Th2. Note that TNFα appears only in the Th1 list. Thus applicant has argued limitations not claimed.

21. Claims 40, 69, and 82 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) in view of Terao et al (of record) in view of Raghupathy et al. (of record) in view of Le et al. (US patent 5,656,272) and in view of Ng et al. (of record) as evidenced by Alak et al. (of record) as applied to claims 1-4, 6-11, 13, 16-19, 29-34, 36, 37, 43-66, 73-79, 86-111, 113-137, and 277-280 above, and further in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) for the reasons of record.

The office action mailed June 27, 2007 states:

> The teachings of Finck, Coulam et al., Raghupathy et al. Le et al., and Ng et al. have been discussed above. These teachings differ from the claimed invention in that they do not disclose the use of the anti-TNF-α antibody CDP870.
>
> Athwal et al. disclose the creation of the anti-TNFα antibody CDP870 (see entire document, particularly Figure 22 and paragraphs 231-266). This antibody is capable of neutralizing TNF-α and is comparable in efficacy to etanercept (see particularly paragraph 262). CDP870 is disclosed as being PEGylated, and as such it has a long plasma half life that is desirable for the treatment of patients (see particularly paragraphs 67 and 26).
>
> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Athwal et al. for the anti-TNFα reagents, such as etanercept, used in the methods of collectively taught by Finck, Coulam et al., Janeway et al., Raghupathy et al., Le et al., and Ng et al. Motivation to make this substitution comes from the teachings of Athwal et al. that increased plasma half life of a reagent is desirable for treating patients and that CDP870 is PEGylated to increase its plasma half life. Therefore, a person of ordinary skill in the art would have been motivated to use CDP870 in place of other TNF-α antagonists because CDP870 has a comparable efficacy to etanercept, and since CDP870 has the advantage of being PEGlylated to increase its half life, thus making CDP870 an ideal reagent for treating patients as taught by Athwal et al.

Applicant's arguments filed December 27, 2007 have been fully considered but they are not persuasive. Applicant argues that independent claims 53 and 73 have been amended to recite additional steps not disclosed by the cited references, specifically measuring a ratio of a Th1 to a Th2 cytokine, the Th1 and Th2 cytokines consisting of TNFα.

This argument is not persuasive because the cited references do disclose measuring cytokine ratios as discussed in the rejection of record. Further, TNFα cannot

logically be both a Th1 and a Th2 cytokine, and this point is evidenced by independent claims 1, 53, and 73 which specifically recited which cytokines are to be considered Th1 and which are Th2. Note that TNFα appears only in the Th1 list. Thus applicant has argued limitations not claimed.

22. Claims 38, 67, and 80 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) in view of Terao et al (of record) in view of Raghupathy et al. (of record) in view of Le et al. (US patent 5,656,272) and in view of Ng et al. (of record) as evidenced by Alak et al. (of record) as applied to claims 1-4, 6-11, 13, 16-19, 29-34, 36, 37, 43-66, 73-79, 86-111, 113-137, and 277-280 above, and further in view of Salfeld et al. (US patent 6,090,382) for the reasons of record.
The office action mailed June 27, 2007 states:

> The teachings of Finck, Coulam et al., Raghupathy et al. Le et al., and Ng et al. have been discussed above. These teachings differ from the claimed invention in that they do not disclose the use of the anti-TNF-α antibody D2E7.
>
> Salfeld et al. disclose the creation of the anti-TNFα antibody D2E7, also known as adalimumab or Humira™ (see entire document, particularly the abstract, Figures 7 and 8, and the bottom of column 2). This antibody is capable of neutralizing TNF-α, does not crossreact with other cytokines and is a human antibody (see particularly columns 9 and 10). Since the antibody is human, it offers the advantage of being less immunogenic and thus is not subject to neutralization by a HAMA response in the therapeutically treated patient (see particularly column 2).
>
> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Salfeld et al. for the anti-TNFα reagents, such as etanercept, used in the methods of collectively taught by Pluenneke, Coulam et al., Janeway et al., Raghupathy et al., Le et al., and Ng et al. Motivation to make this substitution comes from the teachings of Salfeld et al. that their antibody is fully human and thus safer for use in humans since their antibody will not elicit a HAMA response.

Applicant's arguments filed December 27, 2007 have been fully considered but they are not persuasive. Applicant argues that independent claims 53 and 73 have been amended to recite additional steps not disclosed by the cited references, specifically measuring a ratio of a Th1 to a Th2 cytokine, the Th1 and Th2 cytokines consisting of TNFα.

This argument is not persuasive because the cited references do disclose measuring cytokine ratios as discussed in the rejection of record. Further, TNFα cannot

logically be both a Th1 and a Th2 cytokine, and this point is evidenced by independent claims 1, 53, and 73 which specifically recited which cytokines are to be considered Th1 and which are Th2. Note that TNFα appears only in the Th1 list. Thus applicant has argued limitations not claimed.

23. Claims 39, 68, and 81 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) in view of Terao et al (of record) in view of Raghupathy et al. (of record) in view of Le et al. (US patent 5,656,272) and in view of Ng et al. (of record) as evidenced by Alak et al. (of record) as applied to claims 1-4, 6-11, 13, 16-19, 29-34, 36, 37, 43-66, 73-79, 86-111, 113-137, and 277-280 above, and further in view of Adair et al. (US Patent 5,994,510, see entire document) for the reasons of record.

The office action mailed June 27, 2007 states:

> The teachings of Finck, Coulam et al., Raghupathy et al. Le et al., and Ng et al. have been discussed above. These teachings differ from the claimed invention in that they do not disclose the use of the anti-TNF-α antibody CDP571.
>
> Adair et al. disclose the creation of the anti-TNFα antibody CDP571 (see entire document, particularly the abstract and Examples 2-4). This antibody is capable of neutralizing TNF-α and has been successfully used in vivo methods of treatment (see particularly Example 4).
>
> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Adair et al. for the anti-TNFα reagents, such as etanercept, used in the methods of collectively taught by Finck, Coulam et al., Janeway et al., Raghupathy et al., Le et al., and Ng et al. Motivation to make this substitution comes from the teachings of Adair et al. that their antibodies are effective when administered to neutralize TNF-α in vivo.

Applicant's arguments filed December 27, 2007 have been fully considered but they are not persuasive. Applicant argues that independent claims 53 and 73 have been amended to recite additional steps not disclosed by the cited references, specifically measuring a ratio of a Th1 to a Th2 cytokine, the Th1 and Th2 cytokines consisting of TNFα.

This argument is not persuasive because the cited references do disclose measuring cytokine ratios as discussed in the rejection of record. Further, TNFα cannot logically be both a Th1 and a Th2 cytokine, and this point is evidenced by independent

claims 1, 53, and 73 which specifically recited which cytokines are to be considered Th1 and which are Th2. Note that TNFα appears only in the Th1 list. Thus applicant has argued limitations not claimed.

24. No claims are allowable.

25. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Primary Examiner
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